REMARKS

Applicants have amended claim 1 to make explicit that which was implicit, namely, that the specific PDE4 inhibitors are inhibitors of the PDE4 enzyme activity. Support for this amendment can be found throughout the specification, for example at page 17, line 25. To further clarify the type of specific PDE4 inhibitors, Applicants have also amended claim 1 to refer to the PDE enzyme activity inhibitor as a "pharmaceutical agent" as described on page 6, lines 15-18. Applicants have further amended claim 1 to clarify the grammar of the claim as shown. Applicants have amended claim 15 also to clarify the grammar of the claim. These amendments are clerical.

Accordingly, no new matter has been introduced by the amendments and their entry is respectfully requested.

Applicants appreciate the time the Examiner took to meet with Dr. Lerner and the undersigned attorney of record on September 17, 2009. The issues discussed during the interview mainly related to the alleged lack of written description. Specifically, Applicants explained that the terms "specifically inhibits type 4 phosphodiesterase (PDE4)" refers to a known class of small molecules, which has specific characteristics that the skilled artisan would know. The definition of background inhibition relating to the specific PDE4 inhibitors would also be known to the skilled artisan as referring to therapeutic levels. The Examiner also brought up the issue of the breath of the pending claims in view of the description in the specification.

Applicants now turn to the specific rejections.

The Examiner rejected claims 1-7, and 15-16 as allegedly obvious under 35 U.S.C. §103(a) over a U.S. Patent No. 6,294,561 to Fowler et al. ("Fowler") in view of van Kooten et al. (Leukemia and Lymphoma, vol. 12: 27-33, 1993)("van Kooten") and further in view of Jiang et al (PNAS vol. 96: 11236-11241, 1996)("Jiang").

Applicants respectfully disagree and submit that the rejection is improper and should be withdrawn for the following reasons.

Fowler claims benefit of the provisional application No. 60/172,068 **filed on December 23, 1999**. The **present application** claims benefit of the provisional application No. 60/101,721

filed on September 24, 1998. Thus, the present application has benefit of an earlier effective filing date.

Accordingly, Fowler is inappropriately applied as prior art against the present application, and the rejection should be withdrawn.

The Examiner rejected claims 1-7 and 16 as allegedly not complying with 35 U.S.C. §112, first paragraph, written description requirement. The Examiner alleged that the Applicant has not provided evidence that the specific PDE4 inhibitors listed, for example, in Teixeira, do not inhibit PDE1 or PDE3. The Examiner also alleged that the two exemplary PDE4 specific inhibitors used in the examples do not provide a sufficient distinguishing characteristics of the genus of specific PDE4 inhibitors. Further, the Examiner continues to liken the present claims and disclosure to those in question in *Regents of the University of California v. Eli Lilly & Co.*, 119 F3d 1559 (Fed. Cir. 1997)("Lilly"). During the interview, the Examiner also raised a concern, that the claim language would cover, for example, antisense oligonucleotides and interfering RNAs that are not described in the specification.

Applicants respectfully disagree, and submit that the rejection should be withdrawn for the following reasons.

Claim 1 has been amended to make explicit that which was implicit, namely, as discussed throughout the specification, that the specific PDE4 inhibitors covered by the claim are those that inhibit the **enzyme activity** of the PDE4 enzyme. Thus, the claim and definition specifically excludes molecules, such as antisense oligonucleotides or interfering RNAs, because these molecules do not inhibit the PDE4 enzyme activity, but rather prevent expression of the PDE4 enzyme.

Applicants further submit that according to the MPEP 2111, while claims are read broadly before the PTO, the claims must be given a broadest **reasonable** interpretation. *In re Am. Acad. Of Sci. Tech Ctr.*, 367 F3d 1359 (Fed. Cir. 2004) stated that such interpretation must be given "in light of the specification as it would be interpreted by one of ordinary skill in the art". In view of the fact that the specification only discusses and exemplifies pharmaceutical agents in the form of small molecules that specifically inhibit PDE4 enzyme activity, and that the

literature discussing specific PDE4 inhibitors also only describes only small molecules as specific PDE inhibitors, Applicants respectfully submit that one of ordinary skill in the art would interpret the claims to be directed to using specific small molecules that function similarly to rolipram and XX5 PDE4 enzyme inhibitors. Moreover, the specification teaches that the claims require that these inhibitors inhibit the activity of the PDE4, a compound such as antisense oligonucleotides works by preventing expression of the protein.

With respect to the allegation, that Applicants have not provided evidence that the PDE4 specific inhibitors known in the art do not inhibit PDE3 and PDE1, Applicants respectfully submit that Dr. Lerner's 3rd declaration specifically addressed this issue. Dr. Lerner pointed to examples, such as at least two different articles showing that the specific PDE4 inhibitors were known in the art to be PDE4 specific and did not inhibit, for example, PDE3 or PDE1. Fore example, in paragraph 16, Dr. Lerner explained that Trifilieff's (Exhibit J) data also unequivocally confirms PDE4 specificity of four different "specific" PDE4 inhibitors, including NVP-ABE171, Ariflo, V11294A and LAS 31025, and referring to Table 1 at page 243, Id., data showing effect on PDE4, and effect on PDE1, PDE2, PDE3 and PDE5. In paragraph 17, Dr. Lerner pointed to an article by Aoki et al. (Exhibit K) which also confirms that specific PDE4 inhibitors YM976, Rolipram, RP73401, SB207499, and CDP840 also had no effect on PDE1, PDE2, PDE3 or PDE5 referring to Table 1. This was contrasted with a compound, such as theophylline which affects PDE4 but also other PDEs.

With respect to Lilly, the facts of that case are different from the facts in the present application. In Lilly, an unknown compound was being claimes, whereas the present application claims a novel method for using a **known** class of compounds. The Examiner has specifically acknowledged that he "does not dispute that the skilled artisan knows what is presently claimed" (page 6, lines 11-12 of 4/25/09 Office Action). Thus, Lilly does not apply to the facts of the present application.

With respect to the Examiner's question regarding "background level inhibition", Applicants respectfully reiterate the statements made by Dr. Lerner during the interview, namely, that a skilled artisan would know in clinical context what background level inhibition is.

Moreover, as set forth, *supra*, Exhibits J and K make it clear that the known PDE4 inhibitors were specific inhibitors, and that they were considered such by the art.

Moreover as discussed by Dr. Lerner, and as is evident from, for example, Trifilieff, Teixeira, and Aioki, the industry determines specificity of PDE4 inhibitors using comparison to known specific PDE4 inhibitors, such as rolipram, Ariflo, or LAS 31025. Applicants also specifically taught that non-specific inhibitors, such as theophylline are not contemplated in the methods (see, page 7, lines 10-13).

In addition, as described by Dr. Lerner during the interview, the background level inhibition is determined using clinically relevant dosages. This is also evident from the specification, which teaches that the drug dosages must also have clinically tolerable effects (page 24, lines 8-14). Thus, a skilled artisan would consider PDE4 specificity of any molecule in clinically relevant dosages.

In view of the above, Applicants respectfully submit that the claims fully comply with 35 U.S.C. §112, first paragraph, written description requirement, and that the rejection should be withdrawn.

In view of the foregoing, Applicant respectfully submits that all claims are in condition for allowance. Early and favorable action is requested.

In the event that any additional fees are required, the Commissioner is authorized to charge Nixon Peabody LLP Deposit Account No. 50-0850.

Date: September 25, 2009

Respectfully submitted,

/Leena H. Karttunen/

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